Review Article

A Review of Blood-mimicking Fluid Properties Using Doppler Ultrasound Applications

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Abstract

Doppler imaging ultrasound characterization and standardization requires blood that is called blood mimicking fluid for the exam. With recognized internal properties, acoustic and physical features of this artificial blood. Both acoustical and physical merits set in the International Electrotechnical Commission (IEC) scale are determined as regular values, where the components utilized in the artificial blood preparation must have values identical to the IEC values. An artificial blood is commercially available in the medical application and may not be suitable in the mode of ultrasonic device or for rate of new imaging technique. It is sometimes qualified to have the strength to produce sound features and simulate blood configuration for particular implementations. In the current review article, appropriate artificial blood components, fluids, and measurements are described that have been created using varied materials and processes that have modified for medical applications.

Keywords: Acoustical properties, blood-mimicking fluid, Doppler ultrasound, International Electrotechnical Commission, physical properties

Introduction

The blood is considered non-Newtonian when the viscosity relies on shear rate.[1-3] Usually, viscosity depends on the shear rate when tiny vessels of arterial were measured. Furthermore, during the movement of erythrocytes and when the ultrasound beam is scattered from every red cell, it will combine and then the Doppler ultrasound signal becomes clear. Doppler ultrasound imaging has been used widely in many clinical and per-clinical studies.[4,5] The essential drawback of Doppler signal is the noise, which is the output of different varieties of the numbers and methods demands of the sample size within the diffusing elements.[6] Besides blood flow velocity measurements, Doppler ultrasound has also been used for blood aggregation and clot formation studies.[7-10]

Diverse types of blood-mimicking fluid (BMFs) are contained in the literature and are revised by P. Hoskins *et al*. (1990). BMFs usually have a scattering particles material suspended in a fluid such as nylon, polystyrene, starch, and Sephadex.[11-14] The viscosity degree of BMF is suitable for a New-tonian fluid, so, it does not build on shear rate. Blood work as a New-tonian principle that deals within prime (large) vessels.[15] However, to obtain a proper artificial blood, the properties of this blood should be mimic to that of International Electrotechnical Commission (IEC) values with [Table 1].

Artificial blood, which is similar to the features of humans such as density, α, scatter particles, speed of sound and viscosity are commercially available; the range of prices of the Commercial blood is different relying on the size of needed blood. Moreover, commercialized blood is not modified since it is prepared for wide markets and certain applications.[11-13,16-18]

Furthermore, Law *et al*. investigated that BMF properties were diverse via room temperature, humidity, and atmospheric conditions. via room temperature, moisture, and atmosphere pressure. Several of physical and acoustic features, and other examinations with various ways used to develop an artificial blood. The various sorts of admixture liquids and scatter

Received: 10-06-2022 **Revised:** 01-08-2022 **Accepted:** 05-08-2022 **Available Online:** 20-10-2022

Access this article online

Quick Response Code:

Website: www.jmuonline.org

DOI: 10.4103/jmu.jmu_60_22

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How to cite this article: Oglat AA. A review of blood-mimicking fluid properties using doppler ultrasound applications. J Med Ultrasound 2022;30:251-6.

materials utilized in artificial blood production are explained in this article. Artificial blood is made as a particles suspended in the fluids. The diameter of these particles is close to that of real human's RBCs, even though some have a larger diameter than the real human's RBCs.[12,13,19]

The hemodynamic styles of the artificial blood that is applied in vitro by Doppler US should have similar merits as human blood and be easy to prepare. The blood in the US is made of RBCs (erythrocytes). However, the blood is made of different components such as erythrocytes (RBCs), thrombocytes (platelets) and white blood cells (WBCs) (leukocytes). Why is that?

The components of human blood are responsible for significant sides of the Doppler signal. Real blood consists (RBCs) of a suspension material (erythrocytes), thrombocytes (platelets), and WBCs (leukocytes). Because of comparable low numbers of thrombocytes (250,000–350,000) and WBCs (6000–11,000), so, it is supposed that RBCs (5,000,000–6,000,000) are accountable for the scattering of the blood. The normal diameter of the RBCs is 7 μ, and this still less than the wavelength (ʎ) of ultrasound (0.2–0.5 mm). Hence, the sole RBC works like a spot scatter, whose mutual effect is indicated to as Rayleigh-scattering. The blood pulse echo (PE) size is small in comparison to that obtained by the reflection during the interfaces of tissue.[20,21] Based on this view, the preferable liquid to employ is the blood itself. In contrast, there are a specific drawback in applying blood and its components, such as the chance of biohazard. RBCs are easily damaged in vitro due to the ending date of blood is limited (about 120 days). the practice *in vivo* is not ethical and not safe, and this limits the utilization of artificial blood as a standard fluid in several studies of quality monitor. Thus, the concern should be taken to minimize the hazard.[22]

Physical Properties of Blood-Mimicking Fluid

Density

Density is recognized as one of the fundamental factors in BMF because it defines the quantity of mass per unit volume. The particles components applied in the preparation of the artificial blood must be remain suspended (with no float or precipitate) inside a mixture fluid, because it is good to stay neutrally energetic, though at lower velocities. The particle density should be approximately 1.05 ± 0.04 g/cm^3 (1.01–1.09 g/cm^3) close to the human blood density as IEC values.[11-14,16,22]

The density of particles should permit them to be suspended in the liquid, especially when the particles are flowing along the tube. Some researchers reported that the basic issues linked to the particle densities happened when the density is less or much larger than the liquid density. For instance, Figure 1 shows polystyrene scatter particles precipitated in the bottom because its density (1.050·g/cm^3) is greater than mixture fluid (1.030·g/cm^3).[6,11,23] However, several previous studies measured the density of BMF via pycnometer tool.[6,11,12,14,18,19,22-26]

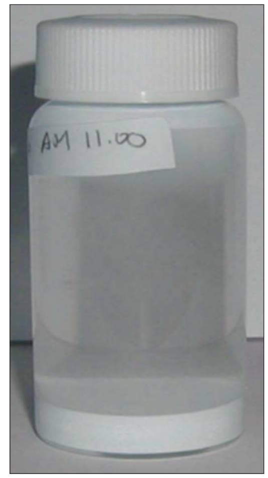

Figure 1: Appearances of the BMF samples in glass jars after 24H. Liquid density: 1.030·g/cm^3, particle diameter: 5 μ. particles settles on the bottom of glycerin and water-soluble silicone oil.[15] BMF: Blood-mimicking fluid

Table 1: Specifications of the blood-mimicking fluid defined as the International Electrotechnical Commission standard[6]

Acoustical and physical properties of BMF	Values
Viscosity (×10^{-3} Pas)	4.0±0.4
Attenuation (dB/cm/MHz)	≤0.1
Acoustic speed (m/s)	1570±30
Density (×10^3 kg/m^3)	1.050±0.040

BMF: Blood-mimicking fluid

Particles' size and their concentrations

Human red cells are concave in shape on both sides [Figure 2]. Particles that are used in BMF are mostly spherical and with a diameter in the range between 5 and 7 μm or 7 and 8 μm to mimic real human red cells.[27] For instant, the particle diameters of polystyrene microspheres are 5–30 μm,[14,23,25,28] 5–20 μm for nylon,[11-13,18,19,22,24,26] and 20–70 μm for Sephadex.[6]

Viscosity

The viscosity of the fluid is a fundamental feature of a liquid; it is linked to the inner friction by the force and it is against the proportional movement between layers gliding past one another. The blood viscosity is considered non-Newtonian *in vivo* in the small arteries and Newtonian *in vitro* because it is anomalous.[29] The main factors that influenced non-Newtonian blood viscosity include temperature, RBCs aggregation, RBCs deformability, shear rate, plasma viscosity, and the hematocrit. Newtonian fluids are fluids that show a fixed viscosity and do not depend on the flow rate and the previous parameters. In other words, Newtonian fluids have a direct relationship between shear rate and shear stress. For example, glycerol, H_2O, blood plasma, and ethanol are Newtonian fluids.[30] The viscosity of the real blood has a direct influence on the vessel speed, especially in small vessels. The velocity increases with an increasing of fluid viscosity, and this happens during preturbulence. And it has the merit of a flow exam target.[31]

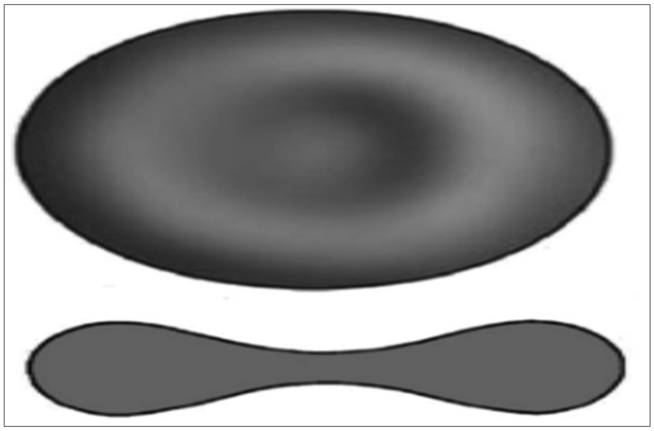

Figure 2: Erythrocyte surface and cross-section[19]

In another study, they found that the dependent on shear rate happen slightly.[32,33] Pedley (1980) stated that blood with an amount of viscosity tested under conditions of maximum shear rate (4 mPa. s) is considered Newtonian in large vessels. The viscosity measurements of human blood with high shear rate were reported as 3.5–4.5 mPa. s at 37°C and with different shear rate 2.25–4.5 mPa.s.[31,34] Moreover, it found that the viscosities of fluids relied on their molecular weight and are proportional to each other.[14]

Changes of shear rate depend on several conditions, for example, the size of vessels and blood stream velocity. However, several researchers measured and calculated the kinematic viscosity and then moved it to viscosity of mixture fluid in the BMF by U-tube viscometers.[12,14,23,25,28]

Acoustical features of Artificial Blood

Sound velocity (SS) and attenuation coefficient (α)

The sound velocity in artificial blood and tissue is usually 1540 m/s.[11-14,17,35] The acoustic velocity in the BMF should be similar (the same ranges to the tubes (Vessel Mimic material [VMM] and tissue) to avoid refraction problems.[12] This problem can be produced with applying tubes and large velocity.[36] For example, Ramnarine *et al*. (1998) investigated that the velocity of blood in draft IEC 1685 standard was reported to be 1570 ± 30 m/s. This huge domain allows the velocity to correspond wall vessel, artificial blood, and the tissue of a flow test object. However, the human blood measurements were done by measure the rate of sound velocity and α,[37] and found that the α of the BMF must be <0.1 dB/cm MHz, and this recommended from the draft of IEC 1685 standard.[35] The range of attenuation coefficient for real blood is <0.1 × 10 − 4× f. Therefore, to decrease inhomogeneity of the velocity range into the tube (VMM), the α of the BMF should be minimal.

A lot of medical researchers have tested both the acoustic velocity and α of the artificial blood by technique called PE signal.[6,11,12,14,18,22-25,38-40] Through a comprehensive previous research study, the speed of sound, α were measured and calculated through the fluid and the solid samples by calculating the time of flight (Tof) of the reflection signal wave pulse using Equations 1, 2a, and 2b, respectively:[11,41,42]

$$\text{SS}=\frac{2(d)}{t} \quad (1)$$

where SS is the velocity of sound of the sample, *d* is depth of the sample (distance), t is the Tof of the reflection signal wave pulse.

$$\alpha=\frac{1}{-D}\,\text{In}\,\frac{Ap2}{Ap1} \quad (2\text{ a})$$

$$\alpha=\frac{2x(dB/cm)}{-D}\,\text{In}\,\frac{Ap2}{Ap1} \quad (2\text{ b})$$

where α is the sample attenuation coefficient, -*D* is the variation in the sample depth in mm, Ap_1 is the signal amplitude (amplitude of transmitted wave), Ap2 is the power signal amplitude (amplitude of received wave), and dB/cm is a constant value and equal to 8.686.

Effect of particles distribution on the velocity profile

Saffman (1956) found that when RBCs diffuse in the vessels, the direction of the particles will be moved toward the center and this because of its force. Kenwright *et al*. (2015) also reported that it is not proper to apply huge particles in tiny vessels because the particles have no ability to take over a tiny part of the diameter and which may have effects on particles diffusing and the sound profile. Though, the influence cannot be noticed. Furthermore, it is important to use small particles and identical to RBSc.[11,14,18] To ensure that the particles concentrations are increasing even for the tiny volume in the narrowing focused beam. It provides a proper blood and helpful at greater frequencies (non-Rayleigh scattering rise because of the large diameter compared to wavelength for large particles). Moreover, to produce an artificial blood that is good in tiny vessels. However, one of the major drawbacks of applying large particles in tiny vessels is the particles aggregation (clotting) inside the flow filed and then producing flow narrowing and stenosis.[6,43]

Backscattering pattern of particles

One of the critical merits of an ability suspension in the artificial blood is constancy and the US backscatter. During utilizing the backscatter of artificial blood in a Doppler application, the object should be entirely known, stable, and reproducible.[17,39] On the other hand, other researchers, Ramnarine *et al*. (2001), Ramnarine *et al*., and Yang and Zhu (2010), indicated that penetration and sensibility measurements are crucial since it should be identical backscatter from the artificial blood and real blood. This backscatter should be known by the draft IEC 1685.[11,13] The relationship between backscattered power and the particles is proportional (linearity relationship). Thus, when particles clot, the backscattered power increase. This influence is recognized for blood.[11,19]

Fast Fourier Transformation (FFT) produces a frequency scope performance of an amplitude obtained in the time range. An immediate measurement and calculation of the separate FFT would be very impressive. Via agents of FFT, it is probable to resolve a time unsteady signal wave into the frequency ranges contained herein and then measure the backscatter power. However, in the past five decades, the FFT was measured and calculated manually by several algorithms, and it was taken more efforts and consuming time for the backscatter power measurements.[44] Currently, there are signal wave processing instrumentations that permit the quick and ease calculation by FFT, like the situation utilized in the current project.[11,17,45]

Walled carotid artery phantoms

Walled phantoms for DU studies are made up of TMM, BMF, and VMM with acoustic properties close to soft tissues, blood, and vessel wall, respectively.[46-50] This means that for a walled phantom, the BMF flows through the VMM. Flow phantoms developed initially were made up of straight tubes designed using shrinking tubes, tapers, or rods.[51-53]

Doppler Ultrasonography of Blood

Doppler technology is a principle that can increase the estimation, diagnostic, and controlling pathologies in blood flow and good for research applications.[54-57] The movement of RBCs away from the transducer is specified by the decline or rise in the ultrasonic frequency. In the Doppler spectrum, evaluation of blood flow in a particular vessel is done by putting a sample-box pointer (sample gate) on the lumen (center) of the vessel, and the spectrum that shows the changes in the velocities through time in cooperation with pulses result from cardiac cycles (motor pump). Moreover, an angle pointer can be applied to show the angle of insonation with the flow direction.[58-60]

Doppler US is a technique used to measure blood speed and flow.[13,61] For example, Ginther and Utt (2004) studied the effect Doppler shift of moving red blood cells at a velocity of 1 m/s toward the vibration pulses transmitted by a US probe, 5 MHz is the US frequency of the probe, and the angle of insonation is˚0. The 5 MHz is equal to 5 × 10ˆ6 Hz. By applying the Doppler shift formula (Equation. 3). The Doppler-shift is positive and approximately is 6493.5 Hz. The Doppler-shift frequencies are in the field of humans audible frequencies and thus can be heard when operated through a speaker.

$$\Delta F_T = 2 (f_o V \cos_\theta / C) \quad (3)$$

where, ΔF_T: Shift frequency (Doppler frequency), f_o: US probe frequency (Hz), V: Blood velocity, Cos ɵ: Cosine angle of insonation, C: Speed sound in S. T which is equal to 1540 m/s.

Doppler signal size based on many factors. First, blood speed: as speed increases, the Doppler signal also increases. Second, the angle of insonation: when the beam of US has much aligned toward the direction of the flow, the Doppler signal will rise (the angle of insonation between the US beam and the flow direction becomes smaller).

Quantitative Doppler Technique

Patterns of blood flow

Measuring the blood flow out of the cardiac and major vessels is done by Doppler tool. For the target of knowing the flow principle in the vessels, it is necessary to understand the variations between the main types of flow, regular (laminar) flow, and disturbed (turbulent) flow. However, when the flow pass through soft equivalent (parallel) lines in the vessel arteries and the RBCs in a region are moving at nearly with the same velocity and same direction, this indicates that this flow is laminar (Figure 2.14 (a)). Whereas, when the flow passes through obstruction or disruption of the normal flow in the vessel arteries, and the RBCs in a region are moving at disorganized velocity and confused direction, this indicates that this flow is turbulent [62,63] [Figure 3].

To know the type of flow, for instance, turbulent or laminar flow, the Reynolds number (R_e) must be calculated by measuring the entrance length (L_o) of VMM by following Equation 4,[12,16,64] and it must be <2100.

$$L_o = 0.04 \times D \times R_e \quad (4)$$

where D is the diameter of the VMM, and R_e is the Reynolds number and its unit-less that specified by this Equation (5):

$$R_e = \frac{dvD}{m} \quad (5)$$

where d is the BMF density (kg/m^3 or g/cm^3), v is the BMF mean velocity (cm/sec), D is the vessel diameter (mm or cm), and m is the BMF viscosity (mPa. s).

Waveform Doppler indices (peak systolic velocity, end diastolic velocity, and time average mean velocity) of blood

The pulse index (PI) and resistive index (RI) can be applied to represent both the elasticity and resistance of downstream blood vessel. The best way to calculate the PI is via subtracting the end diastolic velocity (EDV) from the peak systolic velocity (PSV), then dividing by the time average mean velocity Equation 6; while the RI is calculated utilizing the PSV as the denominator or divisor Equation 7.[63,65,66] Measurements of PSV, EDV, and systolic–diastolic (S, D, or S/D) velocity ratio are significant since the PSV is the primary Doppler parameter to be abnormal in stenosis.[61]

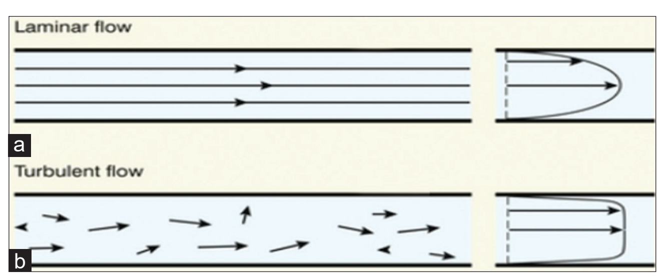

Figure 3: Schematic illustrations and photographs of the (a) laminar and (b) turbulent flow[43]

$$\mathrm{PI} = \frac{(PSV - EDV)}{TAVm} \quad (6)$$

$$\mathrm{RI} = \frac{(PSV - EDV)}{PSV} \quad (7)$$

A normal PSV range in Common Carotid Artery (CCA) should be nearly 60–100 cm/s or 78–118 cm/s or at least to be <125 cm/s; above this range, there may be some stenosis or obstruction occur.[65,67,68] A normal EDV range in CCA should be nearly between 20 and 32 cm/s, the RI between 0.72 and 0.84 cm/s, and PI 0.98–1.94 cm/s.[65,69] The ordinary normal speed of CCA is between 30 and 40 cm/s or 30 and 45 cm/s.[70]

Conclusion

This review article provided brief but comprehensive knowledge on the materials and processes of preparing an artificial blood for DU measurements. Several artificial blood components have been mentioned with diverse features such as attenuation coefficient, viscosity of liquid, particle concentration, the sound velocity, density, and backscatter particles. The components properties guarantee easy to prepare, fit to alter their acoustic features, and is qualified to Produce a normal distribution of scatters.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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